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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/538,985

08/18/2006

Moritz Bunemann

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EXAMINER

PAK, MICHAEL D

ART UNIT

PAPER NUMBER

1646

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/538,985	Applicant(s) BUNEMANN ET AL.	
	Examiner Michael Pak	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 11-23 and 26-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 24 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12-22-06;3-2-07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's election without traverse of group I in the reply filed on November 13, 2008 is acknowledged. SEQ ID NO:12 and 18 elected. Fret pair YFP and CFP elected. G-protein coupled receptor, rhodopsin/beta2 adrenergic receptor-like GPCRs, and alpha2A adrenergic receptor elected. Third intracellular loop CFP and C-terminus YFP elected.

Claim Objections

2. Claims 8, 24 and 25 is objected to because of the following informalities. Appropriate correction is required.

Claim 8 recites acronyms such as GFP, YFP, CFP, BFP and F1AsH which should be modified with the proper name.

Claims 24 and 25 are dependent on non-elected claims which is confusing and can only be examined in part.

Specification

3. The disclosure is objected to because of the following informalities. Appropriate correction is required

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Please review the specification for any other minor informalities.

The specification on page 46 recite the Brief description of the Drawings as figures. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1646

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-10 and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims recite or encompass the terms "human or mouse origin" which is ambiguous and the metes and bounds of the terms are not clear. The claims are not limited by structural limitations and it is not clear when receptor is of human or mouse origin or any other origin because the receptor have mutations which changes the structure of the receptor from the originally isolated receptor. The structural limitations which makes a receptor a mouse or a human or any other species of origin is not known and the metes and bounds is not clear when a receptor meets these structural limitations.

Claims 9 and 10 recite or encompass the term "hybridization" which is a relative term whose metes and bounds are not clear. Hybridization conditions have specific temperature and salt conditions as well as washing conditions. Claims 1-8 and 24-25 encompass the term.

5. Claims 1-10 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for a G-protein-coupled receptor using CFP and YFP to label both third intracellular loop and the carboxy-terminus, does not

Art Unit: 1646

reasonably provide enablement for a seven-transmembrane receptor such as proto-oncogene labeled in both carboxy-terminus and third or first intracellular loop nor does not reasonably provide enablement for any G-protein coupled receptor labeled in both first cellular loop and carboxy-terminus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of § 112 requires that the patent specification enable "those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." Genentech, Inc. v. Novo Nordisk AIS, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)); see also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the

Art Unit: 1646

prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Likewise, in Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), the court affirmed the holding of invalidity of claims to analogs of the EPO gene under § 112 for lack of enablement where applicants had claimed every possible analog of the EPO gene but had disclosed only how to make EPO and a very few analogs. "[D]espite extensive statements in the specification concerning all analogs of the EPO gene that can be made, there is little enabling disclosure of the particular analogs and how to make them There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them." *Id.*, 927 F.2d at 1213-14, 18 USPQ2d at 1027.

Claims encompass all seven membrane receptor including proto-oncogene which is labeled in both carboxy-terminus and third or first intracellular loop. However, one skilled in the art cannot use all seven transmembrane receptor to label the third or first intracellular loop because unlike the G-protein coupled receptors, the labeling with large insert with fluorescent protein into the third intracellular loop or first intracellular loop will sterically disrupt the interaction with G-protein or other functional activator in the intracellular region. Furthermore claims encompass G-protein or other seven transmembrane receptor labeled with both carboxy terminus and first intracellular loop. However, the one skilled in the art cannot use receptors labeled in the first intracellular loop because the large fluorescent protein insert will disrupt the interaction with G-

Art Unit: 1646

protein or other functional activator in the intracellular region. The amount of direction provided in the specification is limited to a specific species of G-protein coupled receptor with CFP and YFP inserted into third intracellular loop and the carboxy-terminus. One skilled in the art would require empirical experimentation in order to determine the effect of inserting CFP and YFP or other fluorescent proteins into other seven transmembrane receptors without disrupting the intracellular structure for the protein activity. Furthermore, one skilled in the art would require empirical experimentation in order to determine the effect of inserting fluorescent protein into the first intracellular loop without disrupting the intracellular structure due to steric hindrance or folding hindrance for the protein activity. The specification does not teach how to use such variant labeled receptors which are functional. Receptors have specific folding with active sites and intracellular active region which are essential for the proper function of the protein in functioning (Kobilka et al., Methods in Enzymology, 2002). The state of the art is such that one skilled in the art cannot predict the outcome of changes to protein structure using large fluorescent protein insertion into important structural domains. Thus, one skilled in the art cannot predict the functional outcome of the insertion of fluorescent protein into domains of the receptor. No working example is provided to determine whether a change in the first intracellular loop would provide proper function. It would require empirical experimentation to determine whether the variants is functional. Thus, such variants encompass a genus with a large number of species which are not functional. In view of the extent and the unpredictability of the experimentation required to practice the invention as claimed, one skilled in the art

Art Unit: 1646

could not make the invention without undue experimentation. Therefore, based on the above Wands analysis, a preponderance of the evidence supports a conclusion that one skilled in the art would not have been enabled to make and use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, 6-7, 9-10 and 24-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Altenbach et al. (Biochemistry, 2001).

Altenbach et al. disclose rhodopsin labeled in the third cytoplasmic loop and the C-terminus with cysteine fluorescently labeled (figure 2; pages 15495-15497).

As discussed above in the 35 USC 112 paragraph 2 rejection above, the term “human or mouse origin” metes and bounds are not clear and the mutation in rhodopsin falls within the claim limitation because it is not in the original form anymore and has many of the characteristics of both human and mouse origin. The nucleotide sequence will always hybridize with another sequence which has a complementary nucleotide.

7. Claims 1-4, 6-7, 9-10 and 24-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Kobilka et al. (Methods in Enzymology, 2002).

Art Unit: 1646

Kobilka et al. disclose human beta-2 adrenergic receptor which has been labeled with poly HIS at the C-terminus and labeled with fluorescent cysteine at the third intracellular loop (pages 172 and 175-179).

The nucleotide sequence will always hybridize with another sequence which has a complementary nucleotide.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak whose telephone number is 571-272-0879.

The examiner can normally be reached on 8:00 - 2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1646

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Pak/
Primary Examiner, Art Unit 1646
March 1, 2009